

# Autonomic effects on the human cardiac conduction system\*

## *Evaluation by intracardiac electrocardiography and programmed stimulation techniques*

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**SUMMARY** After right heart catheterisation in 20 subjects, aged 30 to 82 years, the techniques of intracardiac electrocardiography and programmed stimulation were used to determine variables of normal function of the sinuatrial node, atrioventricular node, and intraventricular conduction system. Specific attention was paid to autonomic influences on these variables. These were assessed by comparison of determinations made before and after cardiac autonomic block induced by intravenous atropine, 0.03 mg/kg, and propranolol, 0.15 mg/kg.

Sympathetic and larger depressant vagal effects on sinuatrial node function (sinus cycle length and sinus node recovery time after overdrive atrial pacing) were demonstrated. Autonomic effects on atrioventricular node conduction (AH interval and Wenckebach threshold to incremental right atrial pacing) were small, of similar magnitude (approximately 20% change), and opposing. Only significant vagal effects in increasing the effective and functional refractory periods of the atrioventricular node (pacing at 100 bpm) were demonstrated (approximately 15 and 12% change, respectively). The atrial effective refractory period, duration of the His bundle electrogram, and the HV interval were unchanged by either drug. Effects on refractory periods of the intraventricular conduction system could not be assessed because exact determinations were limited by refractoriness of the atrioventricular node. The QT interval with pacing at 100 bpm decreased significantly after atropine but was unchanged after propranolol.

The techniques of intracardiac electrocardiography<sup>1</sup> and programmed intracardiac stimulation<sup>2,3</sup> have greatly increased the understanding of normal cardiac conduction. This has facilitated recognition of functional disorders of the sinuatrial node,<sup>4</sup> atrioventricular node, and specialised intraventricular conduction system.<sup>5</sup>

Sinuatrial node function may be assessed by measurement of the sinus node recovery time after a period of overdrive atrial pacing,<sup>6,7</sup> and the sinuatrial conduction time after single induced atrial depolarisations.<sup>8</sup> The atrioventricular node and intraventricular conduction system may be assessed by measurement of intracardiac conduction times,<sup>1</sup> the response to rapid atrial pacing,<sup>9</sup> and refractory periods using programmed stimulation.<sup>2</sup>

The normal limits of these electrophysiological variables, however, have been imprecisely defined. It might be expected that this may reflect, at least in part, variations caused by temporal changes in autonomic influences on the heart. This proposition was advanced by Jose and Taylor,<sup>10,11</sup> who suggested that pharmacological block of cardiac sympathetic and parasympathetic efferent nerves by propranolol and atropine, respectively, allowed observation of the intrinsic heart rate.

This present study aimed to apply Jose's technique to quantify autonomic influences on normal automaticity of the sinuatrial node, atrioventricular node conduction and refractoriness, conduction in the intraventricular conduction system, and ventricular repolarisation (as assessed by the QT interval). To our knowledge, such systematic assessment by administration of both drugs to a large group of normal patients has not

\* Supported by a grant-in-aid of the Life Insurance Medical Research Fund of Australia and New Zealand.

Received for publication 27 November 1979

been previously undertaken. It is expected that the observation of responses after autonomic blockade might allow the development of more sophisticated criteria for the recognition of abnormal function.

## Subjects and methods

### SUBJECTS

Twenty subjects (12 men and eight women, aged 30 to 82 years, mean age 62 years) were studied. Clinical features and investigations, including routine and prolonged electrocardiographic monitoring, had categorised the subjects into two groups. The first (six patients) had either regular narrow QRS tachycardias, observations during electrophysiology study suggesting that these were a result of ectopic atrial tachycardia (two), or re-entry involving the atrioventricular node (one), or they presented with palpitation with no documented or inducible tachycardias (three). The second group (14 patients) had dizzy spells but no apparent cardiac abnormality clinically or during electrophysiology study. Patients with manifest sick sinus syndrome or atrioventricular conduction abnormality, with other medical conditions which contraindicated the use of atropine or propranolol, or with angina which might have been induced by rapid atrial pacing, were specifically excluded. In each case, catheterisation was only performed when the electrophysiology study was considered to be clinically indicated. Written informed consent was obtained after full explanation of the procedure. A full matrix of data was not obtained. Results relate to the total group of 20 patients unless stated.

### CATHETERISATION TECHNIQUES

Cardioactive drugs were discontinued for at least five elimination half-lives. Patients were fasted on the morning of their study and were not routinely sedated. Rarely, intravenous diazepam 2.5 to 5 mg was given in a bolus injection during the procedure.

Electrode catheters were introduced percutaneously into the femoral veins and advanced under fluoroscopic control to intracardiac sites.

(a) A quadripolar catheter was sited in the high lateral right atrium in the vicinity of the sinuatrial node. The proximal and distal electrode pairs were used for recording of the high right atrial electrogram and for atrial stimulation, respectively.

(b) A tripolar catheter was sited across the tricuspid valve to record the His bundle electrogram.

(c) A bipolar catheter was advanced to a right ventricular site where ventricular pacing could be immediately initiated.

Intracardiac electrograms were obtained by filtering out frequencies below 50 Hz and above

500 Hz. Simultaneous recordings of electrocardiographic leads I, II, and VI, and high right atrial, medial right atrial, His bundle, and right ventricular electrograms were made concurrently on a 0.5 in magnetic tape with play-back facilities (Ampex) and on a six-channel direct writing recorder (Elema Mingograph E 141E/A) at paper speed 100 mm/second.

Intracardiac stimulation was performed using a programmable stimulator (Devices Neurolog) that delivered impulses of 2 ms duration and voltage output approximately twice diastolic threshold. The stimulator enabled both fixed rate cardiac pacing at variable rates and introduction of atrial premature beats after every eight atrial paced beats.

During each of the three periods, before drugs, after atropine or propranolol, and after both drugs (atropine + propranolol or propranolol + atropine), the following measurements were made.

(a) Intracardiac conduction intervals:

- (i) Basic sinus cycle length (ms);
- (ii) AH interval (ms) measured from the high-frequency deflection of the medial right atrial electrogram (A) to the onset of His bundle depolarisation (H). This interval is a measure of atrioventricular nodal conduction time; and
- (iii) HV interval (ms) measured from the onset of H to the earliest onset of ventricular activation from any surface electrocardiographic lead or the right ventricular electrogram (V). This measures conduction time through the His-Purkinje tissue.

(b) The sinus node recovery time measured as the time for recovery of spontaneous sinus node activity after 60 seconds of overdrive high right atrial pacing. Sinus node recovery time was measured between the high-frequency deflections of the relevant high right atrial electrograms, and determined five times at each of two atrial pacing rates, 100 and 130 bpm. Determinations were discarded when a junctional escape beat terminated the post-pacing pause. The pooled means of the five determinations for each patient at each pacing rate were used for statistical analysis of the effects of autonomic blockade.

(c) The response to incremental high right atrial pacing. Pacing was started at a rate just greater than the inherent sinus rate and progressively increased by 10 bpm each 30 seconds until atrioventricular nodal Wenckebach resulted (Wenckebach threshold, in beats per minute).

(d) The refractory periods of the cardiac conducting tissue as measured by the extrastimulus technique.<sup>2</sup> Determinations were made at the same

basic rate of atrial pacing, viz 100 bpm. This eliminated variations caused by the cycle length-dependence of cardiac refractoriness.<sup>12</sup>

- (i) Effective refractory period of the atrium = the longest coupling interval of an extrastimulus ( $S_1S_2$ ) which failed to induce atrial depolarisation;
- (ii) Effective refractory period of the atrioventricular node = the longest coupling interval of an induced atrial depolarisation ( $A_1A_2$ ) which failed to propagate to the bundle of His;
- (iii) Functional refractory period of the atrioventricular node = the shortest propagated response to the His bundle ( $H_1H_2$ ) resulting from any coupling interval of the atrial extrastimulus; and
- (iv) Relative refractory period of the intraventricular conduction system = the longest  $H_1H_2$  coupling interval which resulted in either aberrant intraventricular conduction (identified from the surface electrocardiogram leads), or prolongation of intraventricular conduction of the extrastimulus ( $H_2V_2$ ).

(e) The QT interval measured from the last beat of one minute right atrial pacing at rates 100 and 130 bpm. This technique eliminated the need for correction of the QT interval for heart rate.<sup>13</sup> The interval was averaged from the five sequences of atrial pacing and measured from the onset of the QRS complex to the time for return of the T wave to the isoelectric line.<sup>14</sup> Though three approximately mutually perpendicular electrocardiographic leads were deliberately recorded, in general lead II was chosen for more precise measurements.

For each of these measurements the limit of accuracy was considered to be 5 ms.

#### DRUGS

Atropine was administered in an intravenous bolus dose of 0.03 mg/kg then 0.006 mg/kg per 30 min, to produce vagal block. Electrophysiological measurements were started when sinus cycle length had decreased to a stable level, usually after two to three minutes.

Propranolol was used to produce cardiac sympathetic block. The drug was given by intravenous administration of 1 mg/min to a total dose of 0.15 mg/kg. When necessary, a subsequent dose of 0.03 mg/kg was given 30 minutes later. Arterial pressure was monitored at each minute. Electrophysiological measurements were started 15 minutes after administration of the drug.

#### STATISTICAL METHODS

Determinations for all patients in each treatment period were pooled, and results expressed by mean

± standard error of the mean. Student's *t* test for related variables was used for statistical analysis, a *p* value < 0.05 being regarded as significant.

#### Results

The electrophysiological data obtained are summarised in the Table.

Table Summary of electrophysiological variables before and after autonomic block (propranolol plus atropine or atropine plus propranolol)

Variable	Resting	Autonomic blockade
Sinus cycle length (ms)	929 ± 38	791 ± 34
AH interval (ms)	78 ± 5	77 ± 5
SNRT (RAP 100 bpm) (ms)	1121 ± 41	928 ± 42
SNRT (RAP 130 bpm) (ms)	1079 ± 40	955 ± 40
Wenckebach threshold AV node (bpm)	157 ± 7	158 ± 6
ERP AV node (RAP 100 bpm) (ms)	298 ± 19	277 ± 14
FRP AV node (RAP 100 bpm) (ms)	408 ± 19	389 ± 18
QT interval (RAP 100 bpm) (ms)	334 ± 3	325 ± 5
QT interval (RAP 130 bpm) (ms)	314 ± 4	304 ± 5

SNRT, sinus node recovery time; ERP, effective refractory period; FRP, functional refractory period; RAP, right atrial pacing.

#### SINUS CYCLE LENGTH AND INTRACARDIAC CONDUCTION INTERVALS

The effects of cardiac autonomic block on sinus cycle length in all 20 patients are shown in Fig. 1. Vagal effects could be judged by the decrease in cycle length after initial atropine administration (mean decrease 356 ms, *p* < 0.001) and after atropine administration in those who had already received propranolol (mean decrease 243 ms, *p* < 0.001). Sympathetic effects, as judged by the increase in cycle length after initial propranolol administration (mean 89 ms, *p* < 0.05) and after administration to subjects subsequent to atropine (mean 248 ms, *p* < 0.001), were of lesser magnitude. The mean cycle length after cardiac autonomic block of all patients was 791 ± 34 ms (*p* < 0.01 for comparison with resting cycle length).

In three subjects, decrease in sinus cycle length after atropine administration prevented complete determinations of other electrophysiological variables (SNRT, atrioventricular node refractory periods, and QT interval after right atrial pacing at 100 bpm).

Similar treatment enabled analysis of autonomic effects on the AH interval. The AH interval was 78 ± 5 ms before drugs, and 77 ± 5 ms after autonomic blockade. Vagal and sympathetic effects were of similar magnitude. Atropine decreased the AH interval by 15 ms (*p* < 0.01) in nine subjects who received the drug first and by 13 ms (*p* < 0.05) in another nine who had first received propranolol. Propranolol increased the AH interval by 11 ms

( $p < 0.05$ ) in those nine subjects who received the drug first, and by 14 ms ( $p < 0.05$ ) in the seven subjects who had already received atropine. The durations of the His bundle electrogram ( $19 \pm 1.2$  ms) and the HV interval ( $44 \pm 2.5$  ms) were unchanged by administration of either drug.

#### SINUS NODE RECOVERY TIMES

There was no significant difference in sinus node recovery time after atrial pacing at 100 and 130 bpm, either before or after cardiac autonomic block. In Fig. 2, the effects of cardiac autonomic block on sinus node recovery time are shown. Atropine significantly decreased sinus node recovery time by approximately 497 and 398 ms with pacing at 100 and 130 bpm, respectively, and in patients who had first received propranolol, by 320 and 291 ms at 100 and 130 bpm, respectively ( $p < 0.001$  for all four treatments). Propranolol administration increased sinus node recovery time by 80 ms (NS) and 118 ms ( $p < 0.025$ ), with pacing at 100 and 130 bpm, respectively, and in patients who had first received atropine, by 314 ms ( $p < 0.025$ ) and

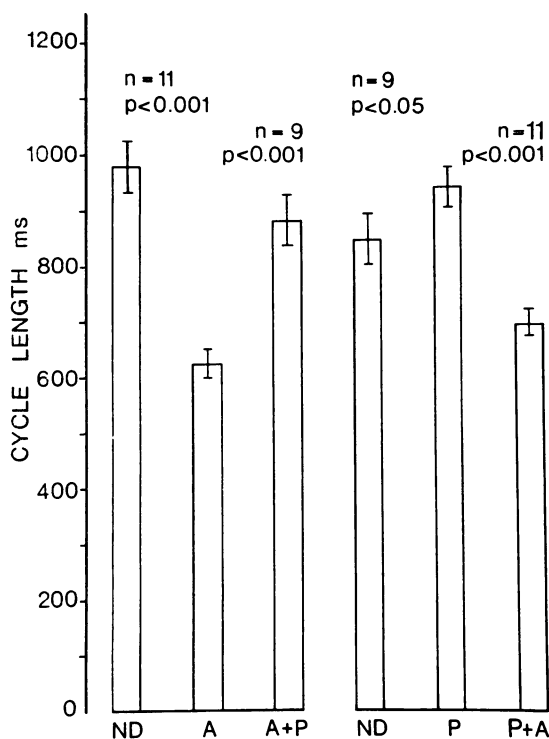


Fig. 1 Sinus cycle length before and after administration of first atropine (A) and then propranolol (P) (to left) and of first propranolol and then atropine (to right). The number of subjects (n) and significance levels for each treatment period are shown.

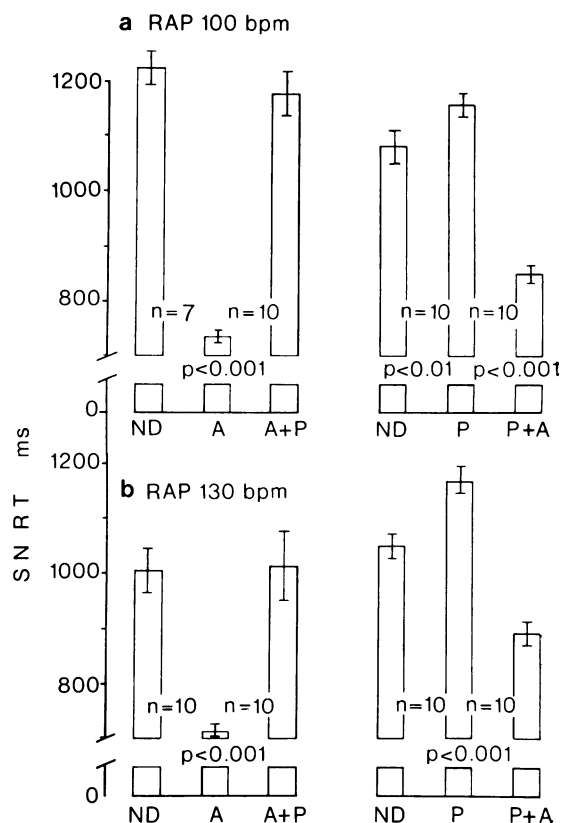


Fig. 2 Sinus node recovery time (SNRT) before and after autonomic block. SNRT was assessed after right atrial pacing (RAP) at 100 bpm (a) and 130 bpm (b).

289 ms ( $p < 0.001$ ) at 100 and 130 bpm, respectively. Vagal effects on sinus node recovery time, assessed by changes occurring after atropine administration, were therefore of greater magnitude than sympathetic effects, measured by changes after propranolol. Thus, sinus node recovery time after autonomic block was  $928 \pm 42$  ms at 100 bpm and  $955 \pm 40$  ms at 130 bpm, both significantly less than before drugs ( $p < 0.001$  and  $p < 0.005$ , respectively).

#### WENCKEBACH THRESHOLD TO RIGHT ATRIAL PACING

In the 16 patients studied, the right atrial pacing rate at which atrioventricular node Wenckebach developed ( $157 \pm 7$  bpm) was no different after administration of atropine and propranolol ( $158 \pm 6$  bpm). Vagal and sympathetic effects respectively increased and decreased the Wenckebach threshold by approximately 20 to 29 bpm ( $p < 0.05$  for all treatments).

## REFRACTORY PERIODS

There were no significant effects of atropine or propranolol on atrial effective refractory periods (ERP) ( $245 \pm 27$  ms) in the 16 subjects tested. Exact determinations of the relative refractory period of the intraventricular conduction system were limited in all subjects by the functional refractory period (FRP) of the atrioventricular node. Because of this, autonomic effects on refractory periods of the intraventricular conduction system could not be assessed.

The effective and functional refractory periods of the atrioventricular node were determined at the same basic pacing rate (100 bpm) in 12 subjects. In these, the effective refractory period of the atrioventricular node was decreased by atropine by 43 ms (those receiving atropine first) and by 55 ms (those receiving propranolol first) ( $p < 0.05$  for both treatments). No significant effects of propranolol were, however, demonstrated. Similarly, only significant vagal effects on the functional refractory period of the atrioventricular node were shown. The functional refractory period of the atrioventricular node was  $408 \pm 19$  ms before drugs. This was decreased by 55 ms ( $p < 0.05$ ) in those initially receiving atropine, and by 41 ms ( $p < 0.05$ ) in those receiving atropine subsequent to propranolol.

## QT INTERVAL

The QT interval was significantly longer with pacing at 100 bpm ( $334 \pm 3$  ms) than at 130 bpm ( $314 \pm 4$  ms) ( $p < 0.001$ ). This difference persisted after autonomic block. Atropine was shown to decrease significantly the QT interval with pacing at 100 bpm ( $p < 0.01$ ) but not at 130 bpm (Fig. 3). No significant effects resulted from propranolol administration.

## Discussion

The doses of atropine and propranolol chosen to induce vagal and sympathetic block were 75 per cent of those thought to be necessary to completely block autonomic effects on heart rate.<sup>11</sup> The difference in intrinsic heart rate in our subjects from those reported by Jose presumably may reflect these different doses. It is planned to compare this normal cohort with patients with disordered function of the sinoatrial and atrioventricular nodes to develop more sophisticated criteria for recognition of abnormalities. Because of this, these lesser doses were chosen after preliminary studies as appropriate to minimise side effects in patients often of advanced age and with other cardiac disease. Other effects of atropine and propranolol, such as antagonism of the nicotinic action of acetylcholine at autonomic

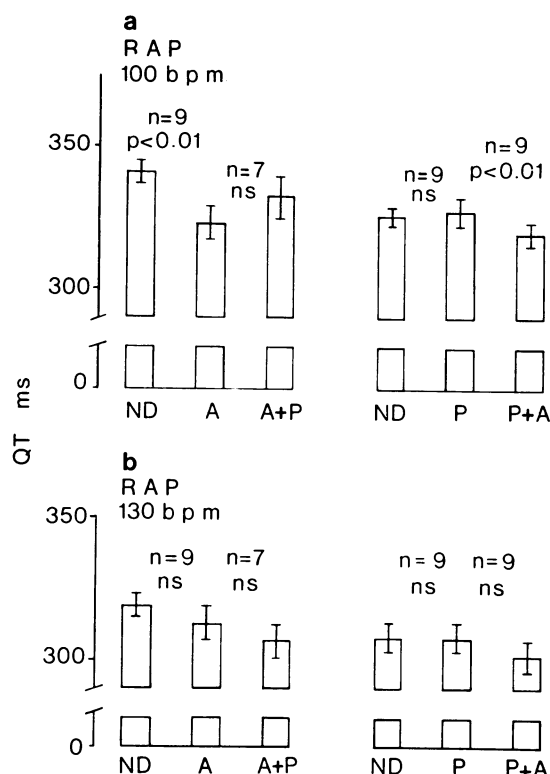


Fig. 3 QT interval before and after autonomic block. Determinations are shown at right atrial pacing (RAP) rates of 100 bpm (a) and 130 bpm (b).

ganglia and production of a degree of cardiac sympathetic block by atropine,<sup>15</sup> and direct and reflex cardiac effects after peripheral adrenergic blockade by propranolol,<sup>16</sup> were assumed to be unimportant.

The choice as to whether atropine or propranolol was initially administered was not randomised. Instead, those patients with an initially longer sinus cycle length usually received atropine first. This attempted to minimise the incidence of tachycardia after atropine which would preclude determination of sinus node recovery time and refractory periods at an atrial pacing rate of 100 bpm. However, those patients with an initially longer cycle length before drugs had a longer cycle length after complete autonomic block. This suggested that the observations reflected a normal distribution of intrinsic heart rates, and that equivalent vagal and sympathetic block was probably achieved.

Autonomic effects on sinoatrial node function can be judged from examination of the effects of atropine and propranolol on cycle length and sinus node recovery time. For both variables, though

both vagal and sympathetic effects were significant and opposing, vagal influences were greater. These effects on cycle length have long been recognised.<sup>17-19</sup> Other electrophysiology groups<sup>20, 21</sup> have examined autonomic influences on cycle length and sinus node recovery time in patients with sick sinus syndrome. They showed a diminished responsiveness of sinus cycle length and a distinct decrease<sup>20</sup> in sinus node recovery time after atropine administration. Isoprenaline rather than propranolol was used to test sympathetic effects in these studies, both normal<sup>20</sup> and subnormal<sup>21</sup> increase in sinus cycle length being reported. Though no normal controls were included in these studies, prolongation of the sinus node cycle length and corrected sinus node recovery time in normal subjects by 0.1 mg/kg propranolol have recently been reported.<sup>22</sup> The vagal influence on normal sinus node recovery time has also been shown.<sup>23</sup> However, in this study, a variable dose of atropine was given (1 to 2 mg, according to age) making quantitative analysis difficult. The decrease in sinus node recovery time after atropine may reflect not only enhanced automaticity, but a decrease in sinuatrial conduction time.<sup>23</sup> Indeed, occasionally a paradoxical lengthening of sinus node recovery time is observed after atropine.<sup>24</sup> This presumably reflects reversal of sinuatrial entrance block and more complete suppression of the sinuatrial node with pacing. This was not observed in any of our patients.

No significant change in effective refractory period of the atrium was shown after autonomic block. Previous reports have been conflicting.<sup>23, 25</sup> It may be surmised that any effects are probably small.

Vagal and sympathetic effects on two variables of atrioventricular node function, AH interval and Wenckebach threshold, were counterbalancing. In absolute magnitude, the changes after either drug were relatively small. The observed normal values for effective and for functional refractory periods of the atrioventricular node are in close agreement with previously published results.<sup>12</sup> Refractory periods of the atrioventricular node, however, were shown to be subject only to significant vagal effects. By contrast, Seides *et al.*<sup>26</sup> were able to show a significant increase of the effective and functional refractory period of the atrioventricular node after the administration of intravenous propranolol (0.1 mg/kg). The explanation for the lack of demonstration of significant sympathetic effects in the present study, using a larger dose, is unclear.

The aspects of intraventricular conduction studied were the HV interval and relative refractory period. No statement as to autonomic effects on the refractory periods can be made from the present

study. However, the absence of effect of atropine<sup>25</sup> and propranolol<sup>26</sup> on HV interval agrees with previous findings.

The observed effects of the drugs on the QT interval are clinically relevant. Variability of the QT interval is well recognised, but studies of the effects of autonomic interactions have been conflicting.<sup>27</sup> Beta-adrenoreceptor blocking agents are advocated to decrease QT in the treatment of ventricular arrhythmias associated with hereditary or drug-induced QT prolongation.<sup>28</sup> Paradoxically, isoprenaline is recommended for the treatment of *torsade de pointes*, a ventricular tachyarrhythmia associated with QT prolongation.<sup>29</sup> Anatomically, the opposing effects of right and left stellate nerve stimulation on the QT interval in experimental animals have been noted.<sup>30</sup> This present procedure showed only small though statistically significant vagal effects on the normal QT interval, and no demonstrable changes after propranolol. Further examination of autonomic effects on the QT interval are apparently necessary.

#### CLINICAL IMPLICATIONS

This study has demonstrated significant vagal and sympathetic effects on clinical electrophysiological variables in a group of normal subjects. The implications for the need for measurement of these variables under steady state conditions, while patients are not subjected to factors such as pain and anxiety, are readily apparent. It is anticipated that abolition of autonomic influences might aid recognition of abnormal pathological conditions as distinct from variable physiological states. The proposition that the statistical power of the electrophysiological observations will be enhanced by autonomic blockade must, however, be examined by a prospective study comparing abnormal and control groups.

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